UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/668,252	03/08/91	WAHL.	

EXAMINER
LOW, C

ART UNIT	PAPER NUMBER
1814	18

18M2/0603

CATHRYN CAMPBELL
PRETTY, SCHROEDER, BRUEGGEMANN & CLARK
444 SOUTH FLOWER STREET STE. 2000
LOS ANGELES, CA 90071

DATE MAILED: 06/03/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

06/03/93

☑ This application has been examined ☒ Responsive to communication filed on 12 March 1993 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 25-28 and 42-55 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 25-28 and 42-55 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office Action.

The amendment and response filed 12 March 1993 is noted. In view of that amendment to the claims, the following grounds of objection and/or rejection are or remain applicable to the pending claims.

The specification remains objected to under 35 U.S.C. 112, first paragraph, as failing to provide a reasonable written description, enablement and best mode for practicing the claimed invention for the reasons indicated in the prior Office Action because the non-human host organism used in the method is not disclosed as to any particular characteristics nor is there an example descriptive of the process defined by claims 25-28. Note that in these claims the non-human host organism is an intact multicellular organism where the specification at pages 1-2 creates doubt as it indicates that manipulation is impaired due to inability to control site of integration, number of copies, temporal expression, and the like. Given these difficulties how is the non-human transgenic host organism which is any nonhuman organism such as a mammal or insect or invertebrate used in the process made so that the FLP target site is not at some random location and what gene is it located in? Before a specific gene can be targeted by DNA which contains the FLP recombination target site (FRT), it must have a specific site for recombination already in the genome of the host. Here, the specification has not indicated any particular transgenic animal where the location of the FLP sites are initially at specific sites predetermined by the user. Note that page 9, lines 10-14 refers to the non-human transgenic animal with the FLP site but does not indicate how the specificity of the placement of the site in the genome is determined or produced, i.e. how is the FLP site for the animal specifically targeted to a specific gene and what portions of that gene are best suited to or for integration of the FLP recombination site? Inasmuch as the non-human mammal contains cells per se, and the FLP site is in the cells, the specification has not provided enabling description for site specific integration of the DNA coding for the FLP site (i.e. the target for the DNA which recombines at the FLP site).

Claims 25-28 and 42-55 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the above objection as indicated in the prior Office Action to the specification.

Applicants comments in the response (pages 6-8) as to the above objection to the specification and rejection of the claims have been considered but are not persuasive. The comments assert that the application has been evaluated as to the background of the application, however, it is pointed out that it is the application itself that produces the above objection and rejection as there is no apparent disclosure of how the FLP site is even targeted to a particular placement of the FLP site in the genome. Moreover, before a specific gene can be targeted by DNA which contains the FLP recombination target site (FRT), it must have a specific site for recombination already in the genome of the host organism or cell and the specification has not indicated any particular transgenic animal or cell where the location of the FLP sites are initially at specific sites predetermined by the user or what cells from what organism already contain the FRT sites. While the DNA to be inserted is targeted to the FRT site, where is that target site as to a specific site in the genome?

Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to host cells in vitro for the reasons indicated in the prior Office Action.

The comments that the amendment makes the rejection moot at page 8 of the response filed 12 March 1993 are noted but not convincing because the claims recite a method applied to intact multicellular organisms; and, indicating that the rejection as moot does not explain where in the specification there is a disclosure of a practicable method as applied to intact multicellular host organisms which still are within the scope of the amended claims. Applicant's amendment to the claim does not remove the issue as set forth in the prior Office Action.

Claims 25-28 and 42-55 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 25, the use of in vitro (lines 1-2) into the genome of a non-human host organism is indefinite as to whether or not the it is the cells from the organism that are genetically altered or whether it is the genome of the intact multicellular organism that is genetically altered which is not the cells of steps i and ii. Cancellation of step iii of the claim is suggested. Claims 43-44 and 50-51 remain indefinite as to the recitation of "within a portion" (claims 43 and 50) as do claims 44 and 52 as to the recitation of a "... second portion ..." and "... at least a portion ..." is unclear. Where is the "first portion"

and what defines "at least a portion"? What portions are referred to, how big is a portion in nucleotide bases (is it one base or $5X10^6$ bases)?

The comments that the amendment makes the rejection moot at page 8 of the response filed 12 March 1993 are noted but not convincing for the reasons indicated above which were set forth in the prior Office Action.

Claims 25-28 remain rejected under 35 U.S.C. 102 (b) as being anticipated by Golic et al. for the reasons indicated in the prior Office Action.

The comments in the response (pages 8-9) filed 12 March 1993 have been considered but are not persuasive as the FLP and FRT in D. melanogaster are compatible in D. melanogaster and the step of mating the flies (page 500), is a step of introducing the cells (the gametes) of one organism into another organism which is also a D. melanogaster gamete which after fertilization becomes a transgenic fruit fly. Note that the claims indicate a non-human host organism and D. melanogaster is a non-human host organism as are its gametes.

Claims 25-28 and 42-55 remain rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic et al. for the reasons indicated in the prior Office Action.

The comments in the response spanning pages 9-11 filed 12 March 1993 have been considered but are not persuasive. The comments as to the Sauer et al. reference as disclosing a different system are noted, however, that is not the reason that the references were combined. As pointed out, Sauer teaches site specific recombination of mammalian cells (col 14+) using plasmids with the DNA coding for the cre and lox (cols 1, 6-7) and although Sauer does not explicitly disclose the use of DNA coding for FLP and FRT, it would have been obvious to one of ordinary skill in the art to use DNA coding for FLP and FRT in vectors for transforming D. melanogaster because Golic et al. disclosed site specific recombination in D. melanogaster with DNA coding for FLP and FRT (see at least pages 499 and 507) which FRT on plasmids can be directed to the site of an FRT already resident in the genome suggesting its use for germline transformation which would have resulted in a transgenic animal. The indication in the reference that "we expect the it will work in other organisms as well" is motivation to to one of ordinary skill in the art to combine the teachings of Sauer which discloses at cols 14+, site specific recombination in mammalian cells (mouse)

where the combination of the Sauer and Golic et al. references would have resulted in a method for site specific recombination in mammalian cells or in transgenic animals. Moreover, where both Sauer and Golic et al. teach that the DNA for the FLP and FRT are from yeast, Sauer teaches at col 5, mating the yeast of opposite mating types which contain the plasmids with the DNA for the FLP and FRT which is a step of introducing the cells produced by the step (i) and (ii) of claim 28 into the subject where the subject is another yeast cell and where Golic et al. disclose mating the flies (page 500), it is a step of introducing the cells which are the male or female gametes into the subject where the subject is the other D. melanogaster gamete which after fertilization becomes a transgenic fruit fly. Note that the FLP and FRT in D. melanogaster are compatible in D. melanogaster and the step of mating the flies (page 500), is a step of introducing the cells (the gametes) of one organism into another organism which is also a D. melanogaster gamete which after fertilization becomes a transgenic fruit fly. Note that the claims indicate a non-human host organism which as claimed is a cell or it can be a D. melanogaster which is a non-human host organism as are its gametes.

Thus, the argument as to the expectation that the yeast DNA would not function in other eukaryotic cells is not convincing because Golic et al. state at page 507 that the system is expected to function in other organisms which is motivation and explicit statement of expectation of success. Applicant also argues speculation, however, an actual successful example is not speculation nor is it hindsight, the allegation of which is not well taken as none was used, implied, asserted, indicated, needed, or inferred. Moreover, the citation of the most relevant art is not hindsight, see In re Winslow, 151 USPQ 48 (CCPA 1966).

Claims 25-28 remain rejected under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic et al. as applied to claims 42-55 above, and further in view of Palmiter et al. as directed to the "non-human host organism" as an intact multicellular animal (i.e. a transgenic animal) for the reasons indicated in the prior Office Action.

The comments as to the Palmiter et al. reference in the response page 11 filed 12 March 1993 have been considered but are not persuasive because it does not consider the teachings of the Sauer (U.S. '317) taken with Golic et al. as indicated in the grounds of rejection. Note that the Golic et al. reference discloses the DNA coding for FLP and FRT (see at least pages 499 and 507) and that FRT bearing plasmids can be directed to the site of an

FRT already resident in the genome suggesting its use for germline transformation which would have resulted in a transgenic animal and further indicate that "we expect the it will work in other organisms as well" which would have motivated one of ordinary skill in the art to combine the teachings of Sauer which discloses at cols 14+, site specific recombination in mammalian cells (mouse) where the combination of the Sauer and Golic et al. references would have resulted in a method for site specific recombination in mammalian cells or in transgenic animals.

No claim is allowed.

Schiestl (US '757) is cited as also disclosing a site specific FRT/FLP recombination system wherein one embodiment utilizes mammalian cells.

The information disclosure statement citing the Senecoff et al., Hartley et al., and Babineau et al. references filed on 12 March 1993 fails to comply with the provisions of 37 CFR 1.97 and 1.98 because there is no certification or indication of payment of fees. See 37 CFR 1.97 (c) and (e). It has been placed in the application file, but the information referred to therein has not been considered on the merits.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

An inquiry concerning this communication should be directed to Christopher Low at telephone number (703) 308-0196.

CSFL

Serial Number 07/ 666,252
Art Unit 1814

02 June 1993

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800